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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,033	08/01/2001	Rosanne M. Crooke	ISPH-0592	5785

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,033	CROOKE ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-26* is/are pending in the application.

4a) Of the above claim(s) *15-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-14 and 20-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

2. Claims 1-2, 4-14, and 20-26 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record. (New Matter)

3. Applicant's arguments filed 11-08-04 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the Examiner's position is noted supported by either factual or legal evidence. Moreover, Applicants cited *In re* Wertheim to traverse this rejection, where the court held that the range of "between 35% and 60%," was supported by the specification, which disclosed the range 25% -60%, and specific examples of 36% and 50%. However, the facts set forth in *In re* Wertheim are not applicable in the instant case. In the instant case, Applicants argue that because Table 1 recites the particular nucleotide numbers according nucleotides 1, 114, and 151, these positions are sufficient to provide support for the end points set forth in the nucleotide ranges of 1-114 and 151-14121. However, on page 89 (lines 17-19) of the specification it defines "target site" as "the 5' most nucleotide number on the particular target sequence to which the oligonucleotide binds." Therefore, the target sites indicated in Table 1 actually define the 5' most nucleotide of a

nucleotide ranges which define particular target sequences, Applicants are interpreting these nucleotide starting points as actual target sequences to design oligonucleotides, when in actuality they represent the 5' most nucleotide number of the target sequence. Therefore, where the Table recites nucleotide 114 as a target site, the Table actually is defining the nucleotide range of 114-133, there is nothing in Table 1 that suggests using nucleotide position 114 as a 3' most end point of a target sequence for designing oligonucleotides, as recited in the nucleotide range of "1-114." The limitation of nucleotides 1-114, do not encompass the nucleotide range of 114-133 are indicated by the "target site" of 114 in Table 1. Moreover, in regards to the nucleotide range of 151-14121, Table 1 recites the "target site" of nucleotide number 151, this target site actually corresponds to the target sequence have a nucleotide range of 151 through 170. The next target site recite in Table 1 is 181, which corresponds to the nucleotide range of 181 through 200. There is no suggestion in Table 1 for designing antisense oligonucleotides targeting nucleotides 171 through 180, which is encompassed by the claimed range of 151-14121. Furthermore, in regards to omitting the nucleotide range of positions 115 through 150 of the nucleic acid molecule encoding apolipoprotein B, there is no support for this omission since Table 1 clearly suggests targeting nucleotides 114 through 133 as indicated by the "target site" of nucleotide number 114, nucleotides 115 through 133 is encompassed by the target sequence of 114 through 133. Therefore, Applicant's omission of these nucleotides from the claimed nucleotide range is also not supported by the specification as originally filed, including Table 1.

4. Whenever new limitations are added to claims, Applicants are required to specifically point out the support for any amendments made to the disclosure. See MPEP § 2163.06 which states, when filing an amendment, an applicant should show support in the original disclosure for

new or amended claims (See MPEP § 714.02 and § 2163.06). As stated in the prior office action, the nucleotide ranges according of 1-114 and 151-14121 of SEQ ID NO: 3, set forth in the claims are considered new matter since the specification as filed does not provide proper antecedent basis for these limitations. No new matter may be included after the filing date of the application. See MPEP § 608.04(b). Applicant is required to cancel the new matter in the reply to this Office Action.

5. Claims 1-2, 4-14, and 20-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description)

In the amendment filed 10-27-03, Applicants amended the instant claims such that all claims recite or are dependent from claims that recite "non-catalytic compound." However, all of the antisense oligonucleotides disclosed by applicant as functioning to inhibit the expression of a nucleic acid molecule encoding apolipoprotein B, as claimed are catalytic. As defined by Webster's II New Riverside Dictionary, "catalytic" is an adjective of "catalyst", "catalyst" being defined functionally as "a substance usually present in small amounts relative to the reactants, that modifies and esp. increases the rate of a chemical reaction without being consumed in the process." A reasonable interpretation of "a non-catalytic compound" would indicate that said compound would not act as a catalyst. However, the antisense oligonucleotides that are disclosed in the specification are encompassed by the term "catalytic" as defined above in that they function in small amounts relative to the reactants to modify the rate of a chemical reaction

(increase the rate of cleavage of mRNA by RNASeH) without being consumed in the process. In addition, antisense as disclosed in the prior art encompasses only antisense that are catalytic. Neither the prior art nor the specification as filed teaches or discloses how an antisense oligonucleotide would be "non-catalytic." Therefore, applicant has not provided a structure of an antisense oligonucleotide that would function as an antisense compound in the method as claimed that is commensurate with the scope of the instant claims drawn to a genus of "non-catalytic compound".

6. In the instant case, the skilled artisan cannot envision the structure of an antisense oligonucleotide that would be a "non catalytic compound" as claimed or the distinguishing identifying characteristics of the genera of "non-catalytic compounds" that would encompass the entire genus. See MPEP § 2163, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." An adequate written description for the invention as claimed requires more than statements that disclose several species of the invention when the claims are drawn to the entire genus. Therefore, applicant has not provided an adequate written description of the invention and the manner and process of making and using said invention such that one skilled in the art would be able to make and use the same.

Claim Rejections - 35 USC § 103

7. Claims 1-2, 4-14, and 20-23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chan et al. (WO 01/12789 A2) in view of Branch, Monia et al., and Agrawal et al. for the reasons of record set forth in the Office Action mailed 1-13-04.

8. The instant rejection is maintained to the extent that the instant claims are drawn to "non-catalytic" compounds, as interpreted by Applicants, wherein the compounds do not function to cleave the target nucleic acid, however function to recruit and/or form the basis for complexes of the target with proteinaceous RNA-cleaving enzymes, i.e. by an antisense mechanism.

9. Applicant's arguments filed 11-08-04 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that everything in the Chan et al. reference is directed to ribozymes, which are a distinct class of molecules compared to the claimed compounds. Applicants point out how the ribozymes of Chan et al. differ from the non-catalytic compounds of the instant invention. In particular, Applicants argue that the parameters for inhibition by non-catalytic compounds are different for the parameters for inhibition by ribozymes. Moreover, Applicants argue that even if a ribozyme inhibited expression of a nucleic acid, one of ordinary skill in the art would not find it obvious that a non-catalytic compound targeted to the same region would successfully inhibit expression of the target nucleic acid.

Contrary to Applicant's assertions, the prior art does teach that antisense and ribozymes are both useful for inhibition of gene expression and both are attractive tools for studying gene function in those systems not amendable to classical genetic analysis. According to Rossi (1993), there are a number of parameters that must be considered for successful utilization of either technique, among these are *(inter alia)* the choice of target, the accessibility of the target to

interaction with a polynucleotide, the intracellular localization of the target and the antisense or ribozyme, the availability of the antisense (ribozyme) for interaction with the target (see page 3, 2nd ¶). In the instant case, the prior art teaching of Chan et al. provides the choice of target, and has demonstrated the accessibility of the target nucleotide of 6679 and its flanking nucleotides to interaction with a polynucleotide. Since Chan et al. teaches the intracellular accessibility of this region of apolipoprotein B mRNA for polynucleotide targeting, it would have been obvious to one of ordinary skill in the art to have assumed that this same region would have also been accessible for antisense oligonucleotides complementary to this region.

Furthermore, since the prior art provides express motivation for designing inhibitors of apolipoprotein B mRNA, and provides the nucleic acid sequence of apolipoprotein B, one of skill in the art seeking to further understand the function of apolipoprotein B would have been motivated to design antisense compounds targeting apolipoprotein B mRNA. As stated previously, Agrawal et al. generally states (regarding the feasibility of utilizing antisense technology), "antisense technology has become an essential laboratory tool to study and understand the function of any newly discovered genes in recent years." Moreover, the prior art (see Monia et al. and Branch) provides extensive guidance for designing antisense compounds targeting a nucleic acid molecule with a known sequence.

As stated in the prior Office Action, absent evidence of unexpected results, it would have been obvious to one of ordinary skill in the art at the time invention was made to modify the teaching of Chan et al. with the teachings of Branch, Monia et al. and Agrawal et al. in the design of the present invention. Chan et al. provide explicit disclosure and motivation for designing a nucleic acid based inhibitor of ApoB mRNA expression. One of ordinary skill in the

art seeking to further understand the role of apolipoprotein B gene expression in cellular processes, would have been motivated to design antisense oligonucleotides targeting the mRNA encoding the *apolipoprotein B* gene, since according to Agrawal, if the sequence of a gene is known, designing antisense oligonucleotides to target that gene would allow the ordinary skilled artisan to further explore and understand the function of that particular gene. Moreover, it would have been obvious at the time the invention was made to substitute the ribozymes targeting apolipoprotein B mRNA with the antisense compounds according to the present invention, since ribozymes and antisense compounds are both nucleic acid based inhibitors, and both function to reduce the expression of a target mRNA as per the teachings of Rossi. It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute one functionally equivalent nucleic acid based inhibitor for another that is to be used for the same purpose, namely for inhibiting the expression of apolipoprotein B mRNA.

Moreover, one of ordinary skill in the art would have been motivated to design antisense oligonucleotides of about 17 nucleotides in length (see Branch) targeting Apo B and comprising the modifications taught by Monia et al. since modified oligonucleotides according to the preferred embodiments of Monia et al. possess a high target site specificity and increased cellular uptake in comparison to unmodified antisense oligonucleotides.

Applicant's arguments do not take the place of evidence, the instant claims remain rejected for the reasons of record.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JLE